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Abstract

Introduction. Advanced and metastatic basal cell carcinomas (BCCs) are rare but still present a severe medical problem. These tumors are often disfiguring and impact the quality of life by pain or bleeding. Based on discovery of the hedgehog (Hh) signaling pathway and it's role in pathogenesis of BCCs, Smoothened (SMO) inhibitors have been developed with Sonidegib being the 2nd in class. It is the only Hh pathway inhibitor investigated in a randomized trial accompanied by pharmacodynamic investigations. Also, the disease assessment criteria applied were more stringent than those used in trials of 1st developed SMO inhibitor – vismodegib, and required annotated photographs, MRI as well as multiple biopsies in case of regression.

Areas covered. All available papers from Medline and the abstracts of the most important dermato-oncology meetings were included.

Expert opinion. Sonidegib is a promising medication for advanced BCC and other malignancies, driven by Hh signaling. It presents favorable pharmacokinetic properties and causes class specific toxicity with dose dependent adverse events in muscular and taste bud homeostasis, gastrointestinal symptoms and hair growth. Early after treatment initiation, it impacts the immunesusceptibility of the tumor lesions. Sonidegib deserves further development in combination with other drugs or antibodies, or alternative dosing schedules.

Keywords

Basal cell carcinoma, Hh inhibitor, SMO inhibitor, sonidegib.

1.1 Introduction

Basal cell carcinoma (BCC) is a skin cancer, considered to originate in the hair follicle. It is the most commonly diagnosed skin cancer and, except for actinic keratosis, the most frequently diagnosed human tumor.

Most BCCs are solitary[1] and, in respect of size, histologic subtype, number and patient characteristics, can be treated with surgery, cryo-, photodynamic or radiotherapy, or using topical medications such as imiquimod or fluoruracil. In rare cases of advanced BCCs systemic therapy, using sonidegib or vismodegib, is indicated. Results of BCC treatment with imiquimod cream, fluoruracil cream and methylaminolevulinate photodynamic therapy (MAL-PDT) were compared in a randomized controlled multicenter trial. After one year of follow up, 72.8% (95 CI 66.8-79.4) of MAL-PDT, 80.1 (95% CI 74.7-85.9) of fluoruracil and 83.4% (95% CI 74.7-85.9) of imiquimod patients were tumor-free [2]. At three year follow up, the results dropped to 58% (95% CI 47.8 – 66.9) in MAL-PDT, to 68.2% of fluoruracil (95% CI 58.1-76.3) and remained stable in imiquimod group, with 79.7% (95% CI 71.6-85.7) of patients remaining tumor-free [3]. Superficial radiotherapy (RT), a treatment option which can be recommended for elderly patients or patients with large facial lesions, showed estimated 5-year recurrence rate of 15.8% in a retrospective setting [4]. These treatment options, although most commonly used for treatment of BCCs, are however inappropriate for treatment of advanced disease. Anatomical location, dimension and morbidity of surgery, makes management of advanced BCCs a real challenge for clinicians.

1.2 Defining advanced basal cell carcinoma

The majority of BCCs are easily cured by surgery. However, a small subset of BCCs are not amenable to either surgery or radiotherapy, thus posing a challenge for clinical management. Complex cases include locally advanced (laBCC) and metastatic BCC (mBCC). As locally

advanced BCC is rare and rather heterogeneous, there is no officially recognized definition of the term. Other terms used in the literature include “severe”, “advanced” and “aggressive” BCC [5]. Advanced BCC sometimes comprises laBCC and mBCC.

A recent analysis of 2938 BCC cases in a Swiss tertiary reference center classified 0.6% of cases as severe with the potential to benefit from Smoothened (SMO) inhibitor therapy. Severe cases were defined as follows: 10 or more diagnoses of BCCs during 5 investigated years, severe clinical progress (including serious complications, BCCs inappropriate for surgery, metastatic BCC) or indication for extensive treatment (including need for resection of noncutaneous structures, surgery combined with irradiation and any systemic treatment) [6].

As there is no standard definition of laBCC, a multidisciplinary panel from the UK defined advanced BCC as “tumors of AJCC stage II or above in which current treatment modalities are potentially contraindicated by clinical or patient-driven factors”. Factors to be considered include clinical factors like tumor size, location, number, tumor subtype, likelihood of successful treatment; and patient-related factors such as age, performance status, Quality of life (QoL) - effects of treatment, patient opinion, the presence of comorbidities and the presence of genodermatoses [5]. Another expert panel developed a grid to analyze the complexity of laBCC using 3 components: factors related to the tumor (location, size, depth, number, symptoms, pathology, history), factors related to operability (curative, reconstruction, recovery, aesthetics) and factors related to the patient (age, comorbidities, competing causes of death, psychological, social and familial context) [7]. Nägeli et al. suggested the following indications for SMO inhibitor treatment: mBCC, laBCC where surgery or RT is not an option, multiple BCCs occurring in patients with genodermatoses such as Gorlin’s syndrome or Xeroderma pigmentosum, BCCs of more than 10 mm diameter or with more than 2 recurrences, BCCs invading bone, muscle or neural structures, BCCs

previously treated with surgery or RT, patients with contraindications to RT, and patients unable to undergo surgery or RT due to comorbidities [8]. As a formal definition is lacking, diagnosis of laBCC usually comprises some degree of subjective clinical judgement.

Metastatic BCC is rare, with reported incidences between 0.0028% and 0.5% [9, 10]. It occurs more frequently in patients with large primary tumors or in patients with primary BCC of a more aggressive histological type (basosquamous, sclerosing, perineural involvement) [10]. Distant metastases commonly occur in the lungs, bone or bone marrow and the skin or soft tissue. Compared to patients with regional metastases, patients with distant metastases are generally younger at mBCC diagnosis, and have a short median survival. Furthermore, patients with bone metastases demonstrate significantly shorter survival than those without, while patients with lung metastases have a significantly longer survival than patients with no evidence of lung metastases [11].

LaBCC and mBCC are a complex and heterogeneous disease and should be treated in a specialized treatment center with an interdisciplinary tumorboard to discuss the best suited, individualized treatment for each patient.

1.3 Pathogenesis

Most, if not all, BCCs demonstrate genetic alterations in genes involved in the Hedgehog (Hh) signalling pathway, resulting in a stem cell like state without terminal keratinocyte differentiation and augmenting BCC's proliferation [12]. The most common alteration is loss of function of patched homologue 1 (PTCH1), which typically inhibits the signalling activity of SMO in the cilium [13]. Gorlin's syndrome is an autosomal-dominant disease, presenting with a variety of developmental disorders and neoplasias, especially BCCs at younger age.

Molecular analysis of patients with the syndrome revealed mutations in PTCH1 gene located on chromosome 9q22[14-16]. Since PTCH1 inhibits Hh signalling pathway, inactivating mutations in PTCH1 lead, through loss of inhibition, to pathway up-regulation and development of a BCC from the stem cells of the hair follicle tissue [17, 18].

Although mutations in PTCH1 are causative for the Gorlin's syndrome and can be identified in majority of the patients, some individuals lack alterations in the gene. Exome sequencing of germline DNA was performed in four unrelated PTCH1-negative individuals from families with Gorlin's syndrome. In three of them, alterations in Suppressor of fused (SUFU) gene were identified [19]. SUFU gene, another factor affecting the Hh signalling pathway, encodes a protein, which negatively regulates the Hh pathway by binding and sequestering glioma associated oncogene (GLI) transcription factors in the cytoplasm [20]. In mammals GLI transcription factors exist in three isoforms, namely GLI1, GLI2 and GLI3, and SUFU binds all [21], thus withholding translocation to the nucleus and induction of expression of cellular differentiation, proliferation and survival regulating genes [20, 22]. Moreover, a case of medulloblastoma, malignancy known to be associated, but rare in Gorlin's syndrome, was documented in all three families with SUFU mutation [19].

2.1 Introduction to the compound

The development of SMO inhibitors was based on the observation that cyclopamine, a substance found in the corn lily, can suppress the Hh pathway and result in birth defects (cyclopia) of sheep [23]. Today, several molecules are in clinical development [24], vismodegib and sonidegib being the most advanced ones that are established treatment options for patients with laBCC, mBCC or Gorlin's syndrome (Table 1) [25].

2.2 Chemistry

Sonidegib (N-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-40-(trifluoromethoxy) biphenyl-3-carboxamide), is selective inhibitor of SMO. It is structurally unrelated to cyclopamine.

2.3 Pharmacokinetics and Pharmacodynamics

Sonidegib had shown high tissue penetration and bioavailability in the preclinical studies [26]. The data collected during Phase I study, demonstrated that median time to maximal plasma concentration (T_{max}) after oral administration is 2 hours (1-48h). Plasma exposure (maximum of serum concentration (C_{max}) and area under the curve (AUC)) after a single 100 to 400 mg dose increases dose-proportionally, for doses above 400 mg the increase is less dose-proportional [27].

A relatively long half-life of 29.6 days [28] might be the consequence of tight tissue and/or plasma protein binding [27]. Sonidegib is a lipophilic drug, whose bioavailability increased five-fold when taken with high-fat food. It is metabolised in the liver, mostly by cytochrome P450 (CYP) 3A4 and excreted mainly with faeces and urine [28, 29].

2.4 Clinical efficacy

2.4.1 Phase I studies

The phase I study was accompanied by translational research that demonstrated a dose-dependent reduction in GLI1 mRNA expression [27]. The maximal tolerated dose (MTD) was 800 mg once daily or 250 mg twice daily. Below the MTD, sonidegib was tolerated well with several low grade (grade 1-2) class related adverse events (AE). 103 patients were included, comprising of 73 and 30 patients on a once- and twice-daily schedule, respectively. 16 patients with BCC and nine patients with medulloblastoma were included in the study population. Grade 1 or 2 AEs occurred in >10% of patients and included muscular (muscle

spasms, myalgia, increase of the serum creatine phosphokinase (CPK) levels), gastrointestinal (anorexia, nausea, vomiting), taste alternating (dysgeusia, ageusia), skin related (alopecia) and constitutional (fatigue) adverse events. Grade 3 or 4 adverse events occurred in <5% of patients and included weight loss, myalgia, hyperbilirubinemia, dizziness and asthenia. The dose limiting toxicity was grade 3 / 4 - serum CPK elevation at a dosage of more than 800 mg once daily or > 250 mg twice daily in 19 of all treated patients (18%). These dose limiting toxicities were observed 3 and 6 weeks after treatment initiating, respectively. Muscular toxicity, based on blood CPK and myoglobin levels without evidence of renal dysfunction, was reported as a dose limiting toxicity in 3 cases. CPK elevation was reversible after treatment discontinuation and appropriate supportive care (sodium chloride or furosemide). 6 of 16 patients with BCC (37.5%) and 3 of 9 patients with medulloblastoma (33%) achieved objective tumour responses [27]. Based on impressive clinical and histological regression of BCCs, a Phase II study BOLT (**B**asal cell carcinoma **O**utcome treated with **L**DE225 **T**reatment) was designed.

2.4.2 Pivotal Phase II study

BOLT is a multicenter, randomized, double-blind, phase II trial (NCT01327053), conducted to evaluate efficacy and safety of sonidegib. In this study, patients with laBCC and mBCC were randomized in a 1:2 fashion to be treated with sonidegib 200 mg (n = 79; laBCC, n = 66; mBCC, n = 13) or 800 mg (n = 151; laBCC, n = 128; mBCC, n = 23) daily. Patients with laBCC were further stratified in respect to having aggressive (micronodular, infiltrative, multifocal, basosquamous or sclerosing) and non-aggressive (superficial and nodular) histological subtypes of BCC [30]. Primary endpoint of the study was objective response rate (ORR), described as confirmed partial response (PR) or confirmed complete response (CR). Target lesion response in mBCCs was determined by central review based on RECIST v1.1 citeria. For laBCCs response was evaluated using a newly designed very stringent assessment

tool called m (modified) RECIST criteria, requiring MRI scan, color photography and histological examination. . Fresh tumor biopsies were taken at screening, week 9, week 17 and at disease progression or in case of complete clinical response. From patients with accessible laBCCs it was also taken at the end of treatment. The number of biopsies taken at each time-point was decided based on the size of the original tumor. As a rule, one biopsy should have been taken from every 4 cm^2 area of the tumor. A CR was only possible, if all three techniques (MRI scan, color photograph and histological examination) showed no tumor tissue. Data analysis was done at 6, 12, 18 and 30 months after randomization of the last patient [30, 31].

Primary endpoint, ORR ≥ 30% (laBCC + mBCC combined), was met at the first data analysis at 6 month after last patient randomization and showed objective response (OR) in 36% (95% CI 25-43) and 42% (95% CI 31-53) of 200 mg and 800mg arms, respectively [30]. After another 24 months of follow up, OR increased to 48% (95% CI 37-60) in 200 mg arm and stayed similar in 800 mg arm (41%, 95% CI 33-49) [31]. When comparing early data and 30 month analysis of OR in laBCC, response rates (RR) were generally better in 200 mg, but improved in both treatment arms (43% and 56% in 200 mg vs 38% and 45% in 800 mg treatment arm) [30, 31]. Different tendency was observed in mBCC group with patients receiving 800 mg showing better, yet unchanged OR at early as well as 30 month analysis (17% and 17% vs 15% and 8% in 200 mg arm) [30, 31]. Response was similar between aggressive and non-aggressive subtypes of laBCC, namely 59.5% vs 55.2% in 200 mg group and 44.0% vs 43.4% in 800 mg [31]. Disease control was seen in over 90% of 200 mg patient population and around 80% of 800 mg patient population at primary analysis [30], and, although at 12-month analysis 77.8% of all patients (73.4% vs 80.1% (200 mg vs 800 mg)) had discontinued the treatment, disease control stayed stable and increased to 92% and 91% at 30 month analysis [31, 32].

Median time to tumor response by central review was similar between the two arms with 4.0 (200 mg daily) and 3.8 months (800 mg daily) [32].

At data cut off for 12-month analysis 77.8 of all patients (73.4% vs 80.1% (200 mg vs 800 mg)) had discontinued the treatment, main reasons being adverse events (25.3% vs 34.4%), disease progression (29.1% vs 9.9%), or patient decision (8.9% vs 19.2%)[32].

2.4.3 Efficacy in patients with Gorlin's syndrome

Efficacy of sonidegib in Gorlin's patients was observed in 2 randomized double-blind studies. In the NCT01350115 trial, 7 patients received 400 mg sonidegib QD and were compared to 2 patients in placebo arm. At week 16, response was clearly better in sonidegib arm with complete histological clearance of main target lesion being 43% compared to 0% in placebo arm. In BOLT trial, 8 patients have reached CR in 800 mg arm (n=13) and none in the 200 mg arm (n=3), nevertheless no treated patients showed progressive disease. AEs' rate (88%) was similar to that observed in patients with sporadic BCCs [33]. These results advocate the using SMO inhibitors not only for treatment but also for cancer chemoprevention.

2.5 Long term outcomes and resistance

Long term data including the key information of cure rates for Hh inhibitors are still limited, the optimal treatment duration is not yet defined and there are already documented cases with acquired resistance to SMO inhibitors' therapy.

Two groups of scientists [34, 35] analyzed vismodegib resistant BCCs and identified, that majority of the relapsed tumors (85%) harbored genetic alterations downstream of PTCH1, most commonly in SMO (50% [34] and 65% [35]), and concurrent copy number changes in SUFU and GLI2, all of which lead to reactivation of the Hh pathway. The SMO mutations were absent in untreated Gorlin and rare (15%) in sporadic BCCs. Four of them, namely SMO-T241M, SMO-I408V, SMO-A459V, and SMO-C469Y, were not detected in the cohort of untreated BCCs, strongly suggesting they could be key drivers in resistance [35]. Moreover,

Atwood et al. identified, that in presence of vismodegib, SMO mutant cells had growth advantage when compared to SMO wild-type tumor cells [34].

Treatment response to sonidegib in patients, with laBCC, resistant to vismodegib, was evaluated in an open label investigator initiated study. Of 9 patients, who were resistant to vismodegib, all were treated with sonidegib and 5 experienced disease progression, three experienced stable disease, in one case response was not evaluable [36]. This, in addition to detection of intra-tumor heterogeneity of resistance mechanisms, suggests that other approaches (itraconazole, arsenic trioxide, IFN α-2b) or new SMO inhibitors (LEQ 506, XL139, Taladegib, TAK-441) could be needed to overcome resistance [24, 35].

2.6 Safety and tolerability

At least one adverse event was experienced by almost all patients in both 200 mg (97,5%) and 800 mg (100%) treatment arms [31], yet 200 mg dose showed more favorable safety profile than 800 mg dose, with less grade 3-4 AEs (43% vs 64%) and AEs leading to dose reduction (32% vs 60%) or treatment discontinuation (22% vs 36%) [30-32]. Most common grade 3-4 AE, increased CPK, was also more frequently observed in 800 mg population (13.3% vs 6.3% in 200 mg). Most common serious AEs, rhabdomyolysis (1.3% vs 3.3%) and increased CPK (1.3% vs 2.7%) were reported by investigators, but none of rhabdomyolysis cases were confirmed by the committee of experts [32]. AEs were the main reason of treatment discontinuation (25.3% in 200 mg and 34.4% in 800 mg treatment arms), in 59% of cases grade 1 or 2 AEs being the cause [32]. A total of 8 in treatment deaths were documented (n=1 in 200 mg and n=7 in 800 mg arms) at 30 month analysis, all reportedly unrelated to the sonidegib treatment [31].

2.7 Comparison between the Hh inhibitors

To date there are no clinical studies comparing efficacy and safety of vismodegib and sonidegib. Given different assessment tools, used in trials of the two drugs, direct comparison of reported efficacy is rather unethical. Despite the less stringent assessment, patients receiving 150mg of vismodegib daily, showed RR, similar to that of sonidegib. At primary analysis, ORR reached 42,7% in laBCC (vs 43% in 200 mg and 38% in 800 mg of sonidegib treatment arms (reference 29)) and 30,3% in mBCC cohorts (vs 17% in 200mg and 15% in 800 mg of sonidegib treatment arms)[13]. After additional 12 months of follow-up, OR of vismodegib receiving patients improved to 47,6% in laBCC arm and to 33,3% in mBCC arm[37].

Similar to sonidegib, most common were class specific toxicities, such as muscle spasms, dysgeusia, alopecia, fatigue and weight loss with all vismodegib receiving patients experiencing at least one, mostly mild, AE. At the time of primary analysis, rate of severe AEs of grade 3 or 4 (most commonly muscle spasms, fatigue, loss of appetite and weight loss) was 31,7% [13]. After additional 12 months of follow up, it increased to 51,9% [37] and was greater than that, observed in patients receiving the approved dosis of sonidegib[32]. As mentioned above, sonidegib was ineffective in patients with advanced BCC, resistant to vismodegib, suggesting that both drugs present comparable class effects.

2.7 Regulatory affairs

Sonidegib (Odomzo®, East Hanover, NJ, USA) is approved by EMA and Swissmedic in a dosage of 200 mg once daily as monotherapy for the treatment of adults with locally advanced basal cell carcinoma[38, 39].

The Food and Drug Administration approved the medication in dosage of 200 mg once daily to treat patients with locally advanced basal cell carcinoma that has recurred following surgery or radiation therapy, or who are not candidates for surgery or radiation therapy[40, 41].

3 Conclusion

The activity of sonidegib in patients with locally advanced and metastatic basal cell carcinoma is good and comparable to vismodegib. The drug seems to be more effective in patients with locally advanced rather than metastatic BCC, has advantage of oral administration, but shows quite high rate of adverse events mostly grade 1 and 2. Results from studies with patients with Gorlin's syndrome illustrate the potential of using of sonidegib not only for treatment but also for cancer chemoprevention. The 200 mg daily dose demonstrates a reasonable benefit/ risk ratio, but since there are no comparative clinical trials, it is not appropriate to make direct comparison to the competitor vismodegib.

4 Expert opinion

BCC is model tumor for a Hh driven malignancy. Most BCC do not metastasize and are curable by conventional treatment approaches. Therefore, the few cases of metastatic BCC open oppurtunities for research. It would be important to understand the key drivers of metastatic disease. There is a good chance that these pathways are discovered in BCCs.

Locally advanced BCCS are not curable by surgery and therefore present a paradigm for the development of Hh inhibitors. In order to investigate the molecular processes involved in tumor regression which might help to improve the therapy outcome, repeated biopsies can be used to monitor the detailed molecular cascades involved. With a superficial large tumor as typically seen in laBCC, this should be feasible. Unfortunately, there was no clear strategy covering this issue in the vismodegib trials. During the BOLT trial biopsies were collected systematically and used for the analysis of GLI expression. However, there is a plethora of other issues that need investigation. Remaining tumor material form clinical trials still remain with the sponsoring companies. These tissues should be offered to research groups acting in the field. We have been able to collect biopsies in only a few patients. Nevertheless, we found

profound alterations in the morphology with an increased keratinization and substantial changes in the microenvironment facilitating local immune responses [42].

In our opinion, early biopsies (within 5 days after treatment initiation) might open additional perspectives on the mode of action.

The final goal for the treatment of BCCs might be a reasonable long term disease control or cure in at least 50% of the patients which implies a series of additional well designed trials. Reviewing the recruitment rates of BOLT and Stevie, these trials are feasible.

Possible treatment combinations have been discussed earlier [24]. However, based on the impact of Hh inhibition on the immune privilege of BCC, combinations with immunostimulants such as interferon, imiquimod or checkpoint inhibitors appear promising and realistic also in the context of the known adverse reaction profiles.

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Table 1. Drug summary box

Drug name (generic)	Sonidegib
Phase (for indication under discussion)	Phase II
Indication (specific to discussion)	Locally advanced or metastatic basal cell carcinoma
Pharmacology description/mechanism of action	selective inhibitor of SMO
Route of administration	Oral
Chemical structure	N-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-40-(trifluoromethoxy) biphenyl-3-carboxamide
Pivotal trial(s)	BOLT[32]